## REMARKS

Opioid drugs, such as morphine, are among the most powerful and widely used analgesics known. These drugs, however, are not without untoward side effects, most notably of which are the sedative and addictive effects of these drugs on the central nervous system (CNS). The present invention provides new opioid drugs that, while retaining activity in the peripheral nervous system, do not substantially affect the CNS, due to the fact that these drugs are less accessible to the CNS. Central to this advantage of these new drugs is the linkage of a charged group, via a spacer, to the nitrogen atom of the basic opioid structure. The charged group, which, by increasing the hydrophilicity of the drug, reduces passage of the drug across the blood-brain barrier into the CNS, has no adverse effects on drug efficiency.

### Summary of the Office Action

Claims 1-25 and 28-30 are pending in this application. Claims 1-14, 17-25, and 28-30 stand rejected under 35 U.S.C. §112, first paragraph. Claims 1-25 and 28-30 stand rejected under 35 U.S.C. §112, second paragraph. Claims 1-7, 17, 18, and 23-25 stand rejected under 35 U.S.C. §102(b). Claims 1-7 and 15-25 stand rejected under 35 U.S.C. §103(a). Applicants address these rejections with the following amendments and remarks.

### Rejection under 35 U.S.C. §112, first paragraph

Claims 1-14 and 17-25 were rejected under §112, first paragraph, with the Examiner stating that the specification does not provide sufficient enablement of the range of compounds defined in the claims. Applicants address this rejection by amendment of the claims.

The Examiner states that claims 1-14 and 17-25 embrace compounds which are not described in the specification but which fall within the scope of the generic

claims. In order to further prosecution of this application, these claims have been amended to call out specific opioids. However, Applicants believe that the claims, as previously written, are allowable and reserve the right to pursue these claims at a later date. In view of these amendments, Applicants request withdrawal of this rejection.

Rejection under 35 U.S.C. §112, second paragraph

Claims 2-4 were rejected under §112, second paragraph, on the basis that the substituents on the various groups are not defined. Applicants address this rejection by amendment of the claims.

The Examiner maintains that claims 2 to 4 are indefinite because the substituents on the spacer are not defined. In order to further prosecution of this application, claims 2 and 3 have been amended to remove reference to the optional substitution, and claim 4 has been cancelled. In view of these amendments, Applicants request withdrawal of this indefiniteness rejection.

Claims 1-14, 17-25, and 28-30 were rejected under 35 U.S.C. §112, second paragraph, for indefiniteness. Applicants address this rejection by amendment of the claims.

The Examiner has rejected claims 1-14, 17-25, and 28-30 on the basis that the term opioids "structurally related to morphine" is indefinite. In order to further prosecution of this application, claims 1, 7, and 18-22 have been amended to remove this language. However, Applicants believe that the claims, as previously written, are allowable and reserve the right to pursue these claims at a later date. In view of these amendments, Applicants request withdrawal of this rejection.

Claim 30 stands rejected under under §112, second paragraph, for indefiniteness. Applicants address this rejection by canceling claim 30.

Rejection under 35 U.S.C. §102(b)

Claims 1-4 were rejected under §102(b) as being anticipated by Hogan (WO Patent No 94-01102-A1). Applicants address this rejection by amendment of the claims.

In order to further prosecution of this application, the independent claims, claims 1 and 18, have been amended to restrict the "charged group" to an amidine or guanidine group. The compound of Hogan does not include an amidine or a guanidine group. Accordingly, Hogan does not anticipate the amended claims. However, Applicants maintain that even without these amendments, the claims are distinguished from the Hogan reference, on the basis that the aminimide group present in the compounds disclosed in Hogan is not a "charged group" a physiological pH. The aminimide group used in Hogan is lipophilic and, therefore, not a group that prevents the compound from crossing the blood-brain barrier into the CNS. Applicants reserve the right to pursue the broader claims encompassing all "charged groups" at a later date. In view of the amendments to the claims, Applicants request withdrawal of this §102(b) rejection.

Claims 1-5, 7, 18, and 23-25 were rejected under 35 U.S.C. §102(b) as being anticipated by Albertson et al. (U.S. Patent No. 4,108,857); Atsumi et al. (U.S. Patent No. 3,950,346); Yokoyama et al. (J. Med. Chem. 22(5):537-553, 1979); Atsumi et al. (JP Patent No. 49-072261-A2); Uwaydah et al. (J. Med. Chem. 22(7):889-890, 1979); and Maeda et al. (Pharmacobio-Dyn. 4(3):167-174, 1981). Applicants address these rejections by amendment of the claims.

The Examiner points out, correctly, that the prior art compounds satisfy the structural requirements of formula II in claim 7. As described above, all of the claims have been amended to restrict the "charged group" to an amidine or guanidine group. Applicants note that none of the references cited in paragraph 5 of the Examiner's Action disclose an amidine or guanidine substituent attached to an opioid. Accordingly, the amended claims are not anticipated by the references

cited above. In view of these amendments, Applicants request withdrawal of these §102(b) rejections.

The Examiner rejected claims 1-7, 17-18, and 23-27 under §102(b) as being anticipated by Jackson et al. (Clin. Exp. Pharmacol. Physiol. 19(1):17-23, 1992). Specifically, the Examiner cites compound (23) on page 22. Applicants address this rejection by amendment of the claims.

Applicants note that the compound cited by the examiner is a disilylmorphine opioid. The independent claims, 1, 7, 18, and 23-25, have been amended to cover a list of specific opioids, which does not include disilylmorphine opioids. Accordingly, the amended claims are not anticipated by Jackson et al. In view of these amendments, Applicants request withdrawal of this §102(b) rejection.

Rejection under 35 U.S.C. §103(a)

The Examiner rejected claims 1-7 and 15-27 under §103(a) for obviousness over Jackson, in view of Green et al. ("Protective Groups in Organic Synthesis," 2nd Edition, John Wiley and Sons, Inc, New York, pages 12 and 77) or Scheinmann (U.S. Patent No. 5,977,326). This rejection should be withdrawn.

The Examiner states that the protected derivative is *prima facie* obvious over the deprotected compound of the present invention, because "one skilled in the art would be motivated to replace Jackson's silyl with the alternative hydrogen as taught by Scheinmann to arrive at the instant invention." Furthermore, the Examiner states that the presence of biological activity in the protected compound is irrelevant to the obviousness of the instant invention. Applicants respectfully disagree.

*The Level of Skill in the Art is not Sufficient to Establish Prima Facie Obviousness*

The Examiner has improperly relied upon the capabilities of one of ordinary skill in the art as motivation to combine Jackson et al. with Green or Scheinmann. Applicants note that there are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art (see *In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998)). Furthermore, the level of skill in the art is not sufficient by itself to establish *prima facie* obviousness (see MPEP 2143.01 and Al-Site Corp. v. VSI Int'l Inc., 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999)).

*The Compound of Jackson et al. Crosses the Blood-Brain Barrier*

The problem to be solved with the present invention is to provide new opioid drugs that, while retaining activity in the peripheral nervous system, do not substantially affect the CNS, due to the fact that these drugs have reduced ability to cross the blood-brain barrier. Regardless of its lack of activity at opiate receptors, compound (23) of Jackson clearly could not solve this problem because the compound was reported to cross the blood-brain barrier. In Jackson et al., the third paragraph of the discussion section, at page 23 column 1, recites:

> "compounds such as (23), in which the guanidino group was attached via a two carbon chain showed low activity *and evidence of breakdown in the body to give CNS activity*." (emphasis added)

Jackson teaches that compound (23), a disilylmorphine derivative with a guanidine substitution at the disilylmorphine nitrogen atom, crosses the blood-brain barrier. Thus, the Jackson reference teaches away from the possibility of solving the problem at hand (preparing peripherally acting analgesics) by making such

substitutions. Motivation to use this approach to make CNS inactive opioid compounds of the present invention is thus not provided by Jackson. There is no motivation to combine the references cited by the Examiner and the rejection should be withdrawn.

*Obviousness Requires a*
*Reasonable Expectation of Success*

The combination of prior art references must provide a reasonable expectation of success (see MPEP 2143.02). The present invention features opioids having reduced CNS activity. Accordingly, at issue is whether the combination of prior art references cited by the Examiner provides a reasonable expection of success for the preparation of opioids having reduced CNS activity. That one skilled in the art would be capable of replacing the silyl protecting groups of compound (23) with hydrogen atoms is not dispositive of meeting the expectation of success. The expectation of success for arriving at the present invention using the combination of references cited by the examiner relies solely upon the biological activity of compound (23) as reported by Jackson et al. As is noted above, the compound of Jackson was reported to cross the blood-brain barrier. In view of this result, there was no reason to have believed that removing the silyl protecting groups would have yielded a CNS inactive molecule, prior to the present invention. There was no reasonable expectation of success. Applicants request that this rejection be withdrawn.

*Jackson et al. is*
*Inoperative Prior Art*

Attached herewith is a declaration by Professor Jackson demonstrating that the synthetic methods disclosed in Jackson for the synthesis of compound (23) could not be repeated (see paragraphs12-19 and Exhibit WRJ-2). Specifically, when the inventors attempted to repeat the synthetic steps to produce the disilyl

compounds disclosed in the Jackson et al reference, they were unable to yield the target compounds. The inventors were then required to construct novel and inventive methods of synthesis, which differed from that taught in the citation in two significant separate ways. These new methods are described in the present application and are the subject matter of claims 19-22. The information provided in the declaration makes it very clear that it would not have been possible for third parties to produce compound (23) using the methods of Jackson et al. It was only when a superior method of synthesis was devised and a better yield of compound was obtained, with acceptable purity, that the inventors were able to carry out a full reevaluation of the functional activities and to arrive at the present invention. Accordingly, the public was not in possession of compound (23) until the methods of the present invention were published. Jackson et al. is inoperative prior art and, therefore, cannot be used to establish a case of *prima facie* obviousness against the present claims.

*The CNS Inactivity of KRS 41*
*is a Surprising Result*

Applicants note that the CNS inactivity of KRS 41, the deprotected form of compound (23), is a surprising result. In the subsequent work conducted by the inventors, it was found that in fact the tributylsilyl-protected derivative was not active at all. In contrast, the deprotected compound, KRS 41, which had not been synthesized previously, not only showed good activity at peripheral opiate receptors, but was CNS inactive (see Professor Jackson's declaration). This result was most surprising in view of the teachings of Jackson et al. and the inventors previous perceptions of the activity of the compounds.

For all of the reasons outlined above, applicants request that the obviousness rejection be withdrawn.

Support for the Amendments to the Specification

Amendments have been made to the second table on page 9, lines 20-25, of the specification to correct clerical errors and include the names of two compounds present in the table. These amendments do not introduce any new subject matter.

Support for the Amendments to the Claims

The claims have been amended to include the limitation that the claimed compounds have reduced or no activity in the central nervous system. Support for this limitation can be found in the specification on page 11, lines 2-3. Furthermore, the claims have been amended to limit Y-N to opioids selected from those listed in Table 1 on pages 9 and 10 of the specification. These amendments do not introduce any new subject matter.

## Conclusion

Applicants submit that the claims are now in condition for allowance and such action is respectfully requested.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: June 5, 2002

Susan M. Michaud

Paul T. Clark
Reg. No. 30,162

Susan M. Michaud
Reg. No. 42,885

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110-2214
Telephone: 617-428-0200
Facsimile: 617-428-7045

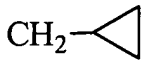
21559
PATENT TRADEMARK OFFICE

50124.005001 reply to OA mailed 12.05.01 final draft

Version with markings to show changes made

The marked-up specification

The second table on page 9, lines 20-25.

| R | X | - or = | R' | R'' | R''' | Name |
|---|---|---|---|---|---|---|
| $CH_3$ | H | = | H | H | Et | Etorphine |
| " | Ac | = | H | H | Et | Acetorphine |
| " | H | - | H | H | Et | [-] Dihydroetorphine |
| " | Ac | - | H | H | Et | [-] Dihydroacetorphine |
|  | H | [=] - | H | H | H | Diprenorphine |
| " | H | [=] - | $CH_3$ | $CH_3$ | $CH_3$ | Buprenorphine |

The marked-up claims

1. (Twice Amended) A compound of formula I:

(Y-N)-(spacer)-([charged group] amidine or guanidine group),

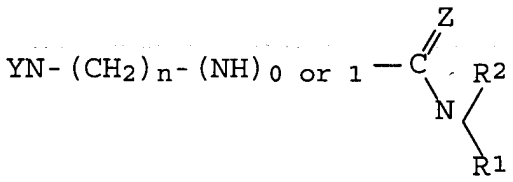
[where said compound has activity at opiate receptors,] wherein Y-N is [an opioid that is structurally related to] an opioid selected from the group consisting of morphine, codeine, heroin, ethylmorphine, O-carboxymethylmorphine, O-acetylmorphine, hydrocodone, hydromorphone, oxymorphone, oxycodone, dihydrocodeine, thebaine, metopon, ethorphine, acetorphine, diprenorphine (M5050), buprenorphine, phenomorphan, levorphanol, pentazocine, eptazocine, metazocine, ethoheptazine, ketobemidone, dihydroetorphine and dihydroacetorphine, and N in Y-N is a nitrogen atom [that corresponds to in position 17] of [morphine]said opioid, to which is linked a spacer, which links said compound to [a charged group] an amidine or guanidine group or a pharmaceutically acceptable salt thereof,

wherein said compound acts as an analgesic, and has reduced or no activity in the central nervous system in comparison to said opioid Y-N.

2. (Twice Amended) A compound according to Claim 1, in which the spacer is a straight or branched alkyl, alkenyl or alkynyl chain of 1 to 6 carbon atoms[,] [which may optionally be substituted].

3. (Twice Amended) A compound according to Claim 1, in which the spacer is a cyclic alkyl, alkenyl or alkynyl group.

7. (Twice amended) A compound according to Claim 1, of formula (II)




(II)

in which YN- represents an organic residue obtained by removal of the R group from an opioid selected from the group consisting of morphine, codeine, heroin, ethylmorphine, O-carboxymethylmorphine, O-acetylmorphine, hydrocodone, hydromorphone, oxymorphone, oxycodone, dihydrocodeine, thebaine, metopon, ethorphine, acetorphine, diprenorphine (M5050), buprenorphine, phenomorphan, levorphanol, pentazocine, eptazocine, metazocine, ethoheptazine, ketobemidone, dihydroetorphine and dihydroacetorphine [structurally related to morphine] of formula (IIIa)

YN-R

(IIIa)

wherein R is H, alkyl of 1 to 6 carbon atoms, or cyclopropylmethyl,

Z is [O, S or] $NR^3$;

$R^1$ is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms;

$R^2$ is H or an alkyl group having 1 to 6 carbon atoms;

$R^3$ is H, alkyl, hydroxy, amino, cyano or acyl, wherein alkyl and acyl have 1 to 6 carbon atoms;

n is an integer of 1 to 6,

and wherein

$R^1$ and $R^3$ may together complete [an addition]a ring,

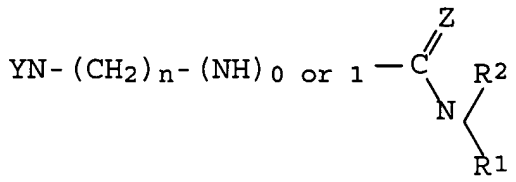
or a pharmaceutically acceptable salt thereof.

12. (Twice Amended) A compound according to Claim 8, in which [Z is NH, and] $R^1$ and $R^2$ are both H.

14. (Twice Amended) A compound according to Claim 12, in which the opioid [structurally related to morphine] is morphine, codeine or buprenorphine.

18. (Twice Amended) A method of reducing the central nervous system activity of an opioid selected from the group consisting of morphine, codeine, heroin, ethylmorphine, O-carboxymethylmorphine, O-acetylmorphine, hydrocodone, hydromorphone, oxymorphone, oxycodone, dihydrocodeine, thebaine, metopon, ethorphine, acetorphine, diprenorphine (M5050), buprenorphine, phenomorphan, levorphanol, pentazocine, eptazocine, metazocine, ethoheptazine, ketobemidone, dihydroetorphine and dihydroacetorphine [structurally related to morphine], comprising the step of linking the nitrogen atom [at position 17] of said opioid [structurally related to morphine] to a spacer group, which in turn is linked to [a charged group]an amidine or guanidine group.

19. (Twice Amended) A method for the preparation of a compound of formula II



(II)

in which

YN-represents an organic residue obtained by removal of the R group from an opioid selected from the group consisting of morphine, codeine, heroin, ethylmorphine, O-carboxymethylmorphine, O-acetylmorphine, hydrocodone, hydromorphone, oxymorphone, oxycodone, dihydrocodeine, thebaine, metopon, ethorphine, acetorphine, diprenorphine (M5050), buprenorphine, phenomorphan, levorphanol, pentazocine, eptazocine, metazocine, ethoheptazine, ketobemidone, dihydroetorphine and dihydroacetorphine [structurally related to morphine] of formula (IIIa)

YN-R

(IIIa)

wherein R is H, alkyl of 1 to 6 carbon atoms, or cyclopropylmethyl,

Z is [O,S or] $NR^3$;

$R^1$ is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 atoms;

$R^2$ is H or an alkyl group having 1 to 6 carbon atoms;

$R^3$ is H, alkyl, hydroxy, amino, cyano or acyl, wherein alkyl and acyl have 1 to 6 carbon atoms;

n is an integer of 1 to 6,

and wherein

$R^1$ and $R^3$ may together complete [an addition]a ring,

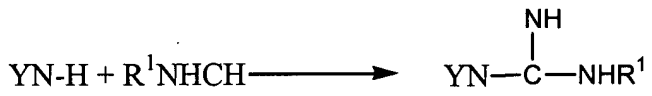
comprising the steps of

(a) Reaction of a compound of formula (IV)

YN-H

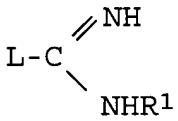
(IV)

with a cyanamide, $R^1NHCN$, according to the equation



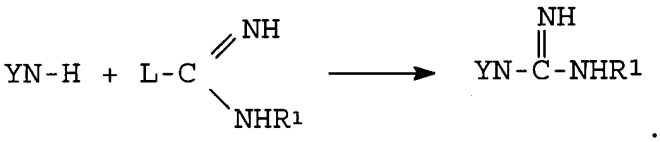
or

(b) Reaction of a compound of formula (IV) with a compound of formula (V)

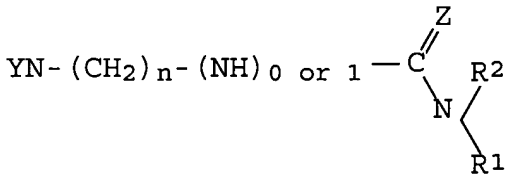


(V)

wherein L is a leaving group, according to the equation



20. (Twice Amended) A method for the preparation of a compound of formula II



(II)

in which

YN-represents an organic residue obtained by removal of the R group from an opioid selected from the group consisting of morphine, codeine, heroin, ethylmorphine, O-carboxymethylmorphine, O-acetylmorphine, hydrocodone, hydromorphone, oxymorphone, oxycodone, dihydrocodeine, thebaine, metopon, ethorphine, acetorphine, diprenorphine (M5050), buprenorphine, phenomorphan, levorphanol, pentazocine, eptazocine, metazocine, ethoheptazine, ketobemidone, dihydroetorphine and dihydroacetorphine [structurally related to morphine] of formula (IIIa)

YN-R

(IIIa)

wherein R is H, alkyl of 1 to 6 carbon atoms, or cyclopropylmethyl,

Z is O, S or $NR^3$;

$R^1$ is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms;

$R^2$ is H or an alkyl group having 1 to 6 carbon atoms;

$R^3$ is H, alkyl, hydroxy, amino, cyano or acyl, wherein alkyl and acyl have 1 to 6 carbon atoms;

n is an integer of 1 to 6,

and wherein

$R^1$ and $R^3$ may together complete an addition ring,

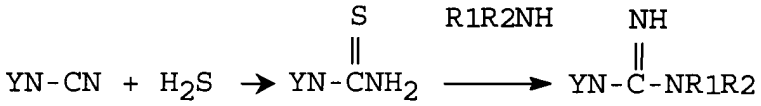
comprising the steps of

(a) Reaction of a compound of formula (VI)

YN-CN

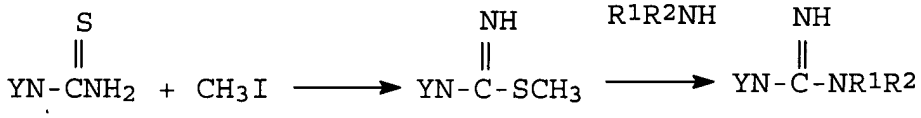
(VI)

with $H_2S$ to obtain an N-thiocarboxamide YN-$CSNH_2$, and optionally reacting the YN-$CSNH_2$ with an amine $R^1R^2NH$ according to the first stage or optionally the two stages of the equation

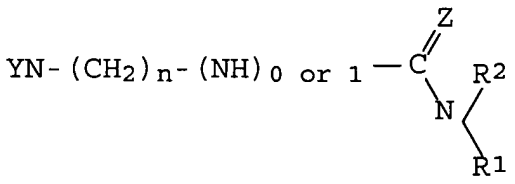



to yield a compound of formula II where Z is S if the optional step is not taken, or a compound of formula II where Z is NH if the optional step is taken, or

(b) Methylating the N-thiocarboxamide to yield an isothiourea compound, which is in turn reacted with an amine $R^1R^2NH$:




21. (Twice Amended) A method of synthesis of a compounds of formula (II)




(II)

in which

YN-represents an organic residue obtained by removal of the R group from an opioid selected from the group consisting of morphine, codeine, heroin, ethylmorphine, O-carboxymethylmorphine, O-acetylmorphine, hydrocodone,

hydromorphone, oxymorphone, oxycodone, dihydrocodeine, thebaine, metopon, ethorphine, acetorphine, diprenorphine (M5050), buprenorphine, phenomorphan, levorphanol, pentazocine, eptazocine, metazocine, ethoheptazine, ketobemidone, dihydroetorphine and dihydroacetorphine [structurally related to morphine] of formula (IIIa)

YN-R

(IIIa)

wherein R is H, alkyl of 1 to 6 carbon atoms, or cyclopropylmethyl,

Z is O, S or $NR^3$;

$R^1$ is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms;

$R^2$ is H or an alkyl group having 1 to 6 carbon atoms;

$R^3$ is H, alkyl, hydroxy, amino, cyano or acyl, wherein alkyl and acyl have 1 to 6 carbon atoms;

n is an integer of 1 to 6,

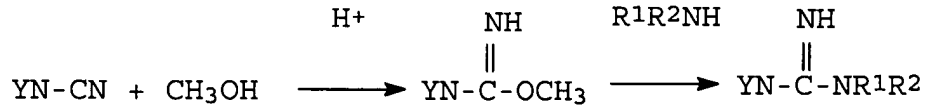
and wherein

$R^1$ and $R^3$ may together complete an addition ring,

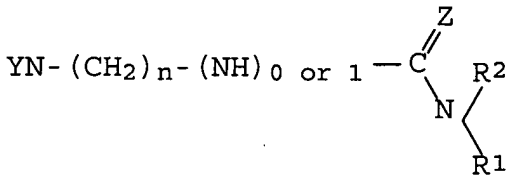
comprising the step of reacting an N-cyano compound of formula (VI)

YN-CN

with methanol under acidic conditions to yield an isourea, which in turn is reacted with an amine according to the equation



22. (Twice Amended) A method of synthesis of a compound of formula (II)



(II)

in which

YN-represents an organic residue obtained by removal of the R group from an opioid selected from the group consisting of morphine, codeine, heroin, ethylmorphine, O-carboxymethylmorphine, O-acetylmorphine, hydrocodone, hydromorphone, oxymorphone, oxycodone, dihydrocodeine, thebaine, metopon, ethorphine, acetorphine, diprenorphine (M5050), buprenorphine, phenomorphan, levorphanol, pentazocine, eptazocine, metazocine, ethoheptazine, ketobemidone, dihydroetorphine and dihydroacetorphine [structurally related to morphine] of formula (IIIa)

YN-R

(IIIa)

wherein R is H, alkyl of 1 to 6 carbon atoms, or cyclopropylmethyl,
Z is NH;

$R^1$ is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms;

$R^2$ is H or an alkyl group having 1 to 6 carbon atoms;

n is an integer of 1 to 6,

and wherein

$R^1$ and $R^3$ may together complete an addition ring,

comprising the step of reacting an N-cyano compound of formula (VI)

YN-CN

and a metallated residue